UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,436	06/07/2001	Sean D. Monahan	Mirus.013.01.01	2612

7590 07/28/2004

Mark K. Johnson
Mirus Corporation
505 S. Rose Road
Madison, WI 53719

EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,436	MONAHAN ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A preliminary amendment filed 06/07/2001 is acknowledged and entered. As a result claims 16-33 are pending and under consideration in this action (See infra, Claim Objections viz., claim numbering).

Specification

Applicant is reminded of the proper content of an abstract of the disclosure. The instant abstract describes a composition and is not reflective of the actual invention, a process for delivery of polynucleotide (e.g. including steps). For example, the disclosure encompasses delivery of naked polynucleotides (or DNA complexed to a polymer) with distinct elements/steps (e.g. increasing blood vessel permeability) but the abstract only makes reference to a complex of DNA and a polymer, for example.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

The foregoing guidelines should be used to correct the Abstract to more properly reflect the true nature of the invention.

In addition, the disclosure is objected to because of the following informalities:

On pages 11 and 32 graphs are present. It is inappropriate for the specification to contain graphs. While applicant's preliminary amendment (filed 06/07/2001) to the specification has appropriately replaced references to the charts therein with figure references (e.g. "Fig. 1" replacing "graph above") and Figs. 1-3 are of record, the amendment does not actually delete the

graphs contained therein. Thus applicant should explicitly amend the specification to remove graphs contained therein. The graphs appear to be duplicates of the figures of record. However, if the graphs are not duplicates then applicant should submit new figures, as deleting any component/element that is not contained in the figures, would be construed as NEW MATTER. Appropriate correction is required.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Therefore, the pending misnumbered claims 1-18 have been renumbered 16-33 (CFR § 1.126).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 16-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claims 16 and 23 recite in parts (e) and (g) respectively that in a method for delivery of polynucleotides or polynucleotide-compound complexes, the methods involve a step of "expressing the polynucleotide". This confers ambiguity to the claims, because it is unclear

whether "expression" is actually a necessary step in a method of delivery. Put another way, parts (e) and (g) do not relate to the preamble. For example, as applicant notes there are factors (e.g. Vascular Endothelial Growth Factor (VEGF); Spec. page 8) that increase permeability. However, the disclosure does not appear to define increasing permeability to actually mean permeability is increased via expression of the delivered polynucleotide. The disclosure references various embodiments for increasing permeability (Spec. pp. 7-8) but not in the context of expressing a permeability effector gene. As written, it is unclear whether the polynucleotide expression is an element/step in delivery of macromoleucles or an intended outcome, which is not necessarily linked with the process of polynucleotide delivery. Therefore, the claims' metes and bounds are indeterminable.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 16 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claims contain subject matter, increasing permeability of mammalian blood vessels, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims read on a broad genus in terms of unspecified step(s), elements or components necessary to increase mammalian blood vessel permeability to facilitate gene delivery *in vivo*.

The genus encompasses disparate components as well as steps, e.g. administering permeability inducing factors, such as VEGF, performing steps to produce permeability inducing conditions, such as *in vivo* injection of hypertonic solutions (e.g. using various ions, such as Calcium or Sodium) or through exogenous gene expression of permeability inducing factors. Therefore, the genus encompasses huge number or combination of components, elements and steps that would be critical for increasing mammalian blood vessel permeability.

The specification provides an example of increasing blood vessel permeability through varying the volume or rate of injection for a liquid solution containing polynucleotides or compound-polynucleotide complexes (e.g. varying hydrostatic pressure of the liquid-borne polynucleotide being injected). There are no detailed components, elements or steps disclosed for other embodiments for increasing blood vessel permeability *in vivo*. The art does not contain any teaching that shows all embodiments for increasing blood vessel permeability *in vivo* to be equivalent or interchangeable. (See, Rekhter et al. Circulation, 1998; 98:1335-41; applying longitudinal mechanical stretching of blood vessels to increase permeability; Muhlhauser et al. Circ. Res., 1995; 77(6):1077-1086; teaching delivery of VEGF via viral vectors to increase vascular permeability; Zunkeler et al. J. Neurosurg. 1996; 8(3):494-502; using mannitol injections to induce vascular permeability). Indeed it appears that different modalities, as disparate as administering a chemical solution versus gene therapy, inhere distinct physiological or biological characteristics.

Because claims 16 and 23 encompass a huge number or combination of steps/components, the skilled artisan would not be able to envision which steps/components correlate with the prescribed function of increasing mammalian blood vessel permeability in a

process of gene delivery to parenchymal cells. Claiming a genus of steps/components necessary to increase blood vessel permeability *in vivo* to effect gene delivery without defining a sufficient number of species as to what specific steps/components will result in increased permeability is not in compliance with the written description requirement.

Given the enormous breadth of the components/steps for increasing blood vessel permeability encompassed by the rejected claims, and given the limited description from the instant specification of such components/steps, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus of components/steps for increasing blood vessel permeability to facilitate delivery of macromolecules. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 16-20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Budker et al. (Gene Therapy, Feb. 01, 1998; 5:272-6; see whole document).

Budker et al. teach delivery and expression of naked polynucleotides in rat muscle cells (i.e. extravascular parenchymal cells) where polynucleotides are injected rapidly and in large volume (increase pressure). (e.g. Abstract; p. 276, ¶ 1). More particularly, the polynucleotides are injected intravascularly. (e.g. p. 272, col. 2, ¶ 2, bottom; p.273, Fig. 1). The critical dependence for permeability is based on the volume and the rate of injection, i.e. increased pressure. (e.g. p. 272, col. 2, ¶ 2; p. 273, Fig. 2). Thus, Budker et al. anticipate the rejected claims.

4. Claims 16-20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (Human Gene Therapy, 1997; 8:1763-72; see whole document).

Zhang et al. teach a process of delivery and expression of naked DNA in mammalian hepatocytes via injected into mammalian blood vessels. (e.g. Abstract). More particularly, Zhang et al. teach using portal vein injections, with occlusion of outflow raising hydrostatic pressure of liquids in the blood vessels. (e.g. p. 1767, Fig. 3; p. 1768, col. 2, 2d full ¶ bridging to p. 1770; p. 1768 Table 1, under last three columns). Therefore, Zhang et al. anticipates the rejected claims.

5. Claims 16-17 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Mann et al. (US 5,922,687; see whole document; hereinafter '687 patent).

The '687 patent teaches a method of delivering polynucleotides using pressure. (e.g. Abstract). More particularly, increased pressure causing increased vascular permeability is used

to transfect rat kidney cells *in vivo*. (e.g. col. 12, Example 5; Fig. 11). Therefore, the '687 patent anticipates the rejected claims.

6. Claims 16-17 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Stedman (US 6,177,403 B1; see whole document; hereinafter '403 patent).

The '403 patent teaches process of delivering vector DNA to extravascular tissue utilizing pressure as well as vascular permeability enhancing agents. (e.g. Abstract). More particularly, vector DNA is injected intravascularly under conditions of varying pressure resulting in delivery (transfection) with subsequent reporter gene expression. (e.g. col. 18, ll. 30-64; col. 21, Table 1; col. 22; ll. 5-40). In sum, the '403 patent anticipates the rejected claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. **Claims 23-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,379,966 (hereinafter the '966 patent).**

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the reference claims. For example, instant base claim 23 is drawn to delivery of polynucleotide-compound complexes to extravascular parenchymal cells. Reference claims 1 and 11 are also drawn to delivery of polynucleotide-compound complexes to extravascular parenchymal cells but differ from slightly (e.g. reference claim 1, part (a) recites "mixing", where instant claim 23, part (a) recites "making"). Therefore, but for the semantic differences between the claims, both instant applicant and reference claims are drawn to biologically and nearly indistinguishable subject matter. As such the reference claims anticipate the instant claims, thus the instant claims are necessarily obvious over the reference claims.

8. **Claims 23-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 10/085,378.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other, because but for semantic differences, instant claims and reference claims are drawn to patentably indistinguishable subject matter, as noted above. Furthermore, the reference claims are drawn to a narrower limitation with respect to the types of cells that are targeted for delivery (e.g. reference claim 1, "muscle cell"; reference claim 14,

"liver cell"). As such the reference claims are a species or sub-genus of the broader instant claims. In this regard, the instant claims fully encompass the reference claims. Furthermore, one of ordinary skill in the art, in examining the full disclosure of the reference application to better practice the invention, would be appraised of the fact that liver and muscle cells are "parenchymal cells". In other words, one of skill in the art may recognize that "parenchymal" is merely a generic term for extravascular muscle or liver cells. The reference claims anticipate the instant claims thus the instant claims are necessarily obvious over the reference claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ray Akhavan
AU 1636

GERRY LEFFERS
PRIMARY EXAMINER